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TITLE: Targeted Alteration of Dietary Omega-3 and Omega-6 Fatty Acids for the Treatment of Post-Traumatic Headaches

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CONTRACTING ORGANIZATION: Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Post-traumatic headache (PTH) is a common problem in military personnel due to their high rate of traumatic brain injury (TBI). From a prior study in migraine we demonstrated that a high Omega-3/low Omega-6 (H3-L6) diet intervention reduced headache pain, altered circulating anti- and pro-nociceptive lipid mediators and their precursor fatty acids, reduced psychological distress and improved quality-of-life in a chronic headache population. We propose to carry out a 2-arm, parallel group, randomized, controlled 12-week dietary intervention trial to evaluate the biochemical effects and therapeutic efficacy of two dietary interventions (one high in Omega-3 and the other high in Omega-6, reflecting the usual US diet) in patients with PTH that are migrainous. We hypothesize that compared to the Control Diet (high Omega-6, low Omega-3), the H3-L6 intervention will produce significant increases in anti-nociceptive n-3 metabolites including 17-hydroxy DHA (Primary Biochemical Aim), and reductions in pro-nociceptive n-6 metabolites. Further, we hypothesize that compared to the Control Diet, the H3-L6 intervention will produce significant improvement in the Headache Impact Test—(a headache-specific quality of life measure-Primary Clinical Outcome), mean total Headache Hours per day, and mean Severe Headache Hours per day.

15. SUBJECT TERMS

Post-traumatic headache (PTH), traumatic brain injury (TBI), nociceptive neurotransmission, migraine, chronic inflammation, biomarker, Omega-3, Omega-6, Headache Impact Test (HIT), nutritional intervention

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION:

Post-traumatic headache (PTH), a common and debilitating secondary headache disorder, is a common problem in military personnel due to their high rate of traumatic brain injury (TBI). Most PTHs have a phenotype indistinguishable from primary headache disorders and have similar responses to therapy. Recent studies indicate that migraine is the most common headache type after trauma, accounting for 50-60% of all PTH, while tension-type headaches account for less than 20%. The mechanisms of PTH are complex and incompletely understood but recent studies emphasize the role of inflammation, cytokine modulation, microglial activation, and abnormalities in neurotransmitter activity in mediating PTH. These observations provide one mechanism underlying the proposed use of dietary interventions designed to reduce chronic inflammation and promote anti-nociceptive neurotransmission, and biomarker data we will obtain will provide direct support for the role of inflammation in PTH. From a prior study in migraine we have preliminary data demonstrate that a high Omega-3/low Omega-6 (H3-L6) diet intervention reduced headache pain, altered circulating anti- and pro-nociceptive lipid mediators and their precursor fatty acids, reduced psychological distress and improved quality-of-life in a chronic headache population. These compelling preliminary data also help establish the feasibility of implementing this dietary intervention in TBI populations with chronic pain. We propose to carry out a 2-arm, parallel group, randomized, controlled 12-week dietary trial to evaluate the biochemical effects and therapeutic efficacy of two dietary interventions (one high in Omega-3 and the other reflecting the usual US diet, high in Omega-6) in patients with PTH with migrainous phenotype. We hypothesize that compared to the Control Diet (high Omega-6, low Omega-3), the H3-L6 intervention will produce significant increases in anti-nociceptive n-3 metabolites including 17-hydroxy DHA (Primary Biochemical Aim), and reductions in pro-nociceptive n-6 metabolites. Further, we hypothesize that compared to the Control Diet, the H3-L6 intervention will produce significant improvement in the Headache Impact Test—a headache-specific quality of life measure-Primary Clinical Outcome); mean total Headache Hours per day; and mean Severe Headache Hours per day.

2. KEYWORDS: Provide a brief list of keywords (limit to 20 words).

Post-traumatic headache (PTH), traumatic brain injury (TBI), nociceptive neurotransmission, migraine, chronic inflammation, biomarker, Omega-3, Omega-6, Headache Impact Test (HIT), nutritional intervention

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Task 1: Planning and Regulatory Review (Months 1-5)

Subtask 1a. Complete the detailed protocol, Standard Operating Procedures (SOP) manual, develop Case Report Forms (CRFs), create and beta test Database, create study website. Trial registration in Clinicaltrials.gov. Advertise for and hire study staff.

Subtask 1b. Obtain IRB approvals at WRNMMC, USUHS, NIH, UNC-Chapel Hill, and Womack Army Medical Center.

Subtask 1c. Training of dietitians, and standardize preparation of diets.

Subtask 1d. Training of study staff at all sites.

Subtask 1b has not yet been obtained due to significant WRNMMC IRB delays

Task 2. Start recruitment and enrollment of patients at all sites (Months 6-12)

*Subtask 2a***.** Target is that all sites will have enrolled at least 1 participant by the end of Year 1. Target is that all sites combined have enrolled at least 20 participants.

Subtask 2b. All sites will have had 1 monitoring visit to insure adherence to protocol and that all study procedures are being carried out uniformly and efficiently.

2c. At the end of Year 1, biochemical assays on participants enrolled over the first 6 months will be performed to ensure that sample quality is excellent and that anticipated values are obtained.

Task 3. Continue patient recruitment and enrollment (Months 13-24)

Subtask 3a. Anticipate that at the end of Year 2, 70 participants will have been enrolled at the three clinical sites.

Subtask 2b. Once enrollment is active at each site, monitoring visits q 6 months to insure adherence to the protocol and that all study procedures are being carried out uniformly and efficiently.

2c. Complete biochemical assays on participants enrolled in the first half of the study. Prepare first ript for publication on the association of baseline PTH characteristics with plasma levels of bioactive

Task 4. Continue patient recruitment and enrollment (Months 25-36)

Subtask 3a. Anticipate that at the end of Year 3 110 participants will have been enrolled at the three clinical sites.

Subtask 2b. Continue monitoring visits q 6 months to insure adherence to the protocol and that all study procedures are being carried out uniformly and efficiently.

Subtask 2c. Complete biochemical assays on participants enrolled in the first three years of the study. Prepare second manuscript for publication on the association of baseline post-concussive symptoms, mood, affective, and cognitive problems, and plasma levels of bioactive lipids.

Task 5. Complete all study procedures (Months 36-40)

Subtask 5a. Complete enrollment of 120 participants, including followup after 12 weeks of dietary intervention.

Subtask 5b. Resolve all data queries originating from data monitoring visits.

Subtask 5c. Complete biochemical assays for entire study.

Task 6. Data analysis and preparation of primary manuscripts. (Months 40 – 48)

Subtask 6a. Complete data cleanup and database lock.

Subtask 6b. Complete analysis of primary and secondary outcomes.

6c. Prepare manuscripts for publication for primary outcome and secondary outcomes.

3. ACCOMPLISHMENTS:

What was accomplished under these goals? A DSMC with new stoppage rules established at UNC

1. Received full WRNMMC parent/shell multi-site protocol approval 16 FEB 2016
2. First level IRB approval for all site-specific protocols, including WRNMMC, FBCH and WAMC and UNC as the data center was approved by the WRNMMC IRB, with modifications approved 9-23-2017.
3. Second level HRPO approval for all site-specific protocols, including WRNMMC, FBCH, WAMC and UNC approved 25 JUL 2016, 10 JAN 2016, 10 JAN 2017 and 22 DEC 2016, respectively. HRPO Second Level Approval from: Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US) Date: Jan 10, 2017 Subject: A-18878.d Approval Memorandum (Proposal Log Number PR141560, Award Number W81XWH-15-2-0059)
4. FITBIR and UDEs for study CRFs and FITBIR transfer complete.

5. A DSMC with new stoppage rules established at UNC for study monitoring and safety oversight.
6. New FBCH PI, Melissa Guerra, MD, added to the protocol 9-23-2017.
7. Assay equipment for NIH fat metabolite assays acquired.
8. Research personnel hired and trained.
9. Registered on ClinicalTrials.org, NCT03272399.
10. Monthly conference calls among the 5 campuses have been held by Dr. Kenney.
11. We identified and have a contract with a food company from which to purchase the food to be prepared by the kitchens for the study.
12. All blood processing equipment has been purchased and dispensed to sites, including phlebotomy supplies and labels for cryovials.
13. Freezers and shelving for food are in place at the sites.
14. Web-based randomization and data entry system (RedCap) and FITBIR forms are complete.
15. A CRADA has been completed between WRNMMC and HJF.
16. An MTA has been executed for transfer of samples from WRNMMC to NIA, NIH for planned study analysis.
17. A newly required (WRNMMC DRP) Data Sharing Agreement DHA is ready for signatures.
18. All training for study staff, phlebotomists, processors, Investigators, data entry personnel, and dieticians has been completed.
19. GCP training certificates were collected from all study staff.
20. The Continuing Review due 12-2017 to the WRNMMC IRB for review is ready for submission by the PI.
21. Recruitment and enrollment of patients began at all enrolling sites in year 2 (4 at WAMC, 2 at FBCH and 1 scheduled at WRNMMC as of 30 SEPT 2017).
22. Now that enrollment is active at each site, monitoring of the Headache Diary and protocol adherence will be monitored bi-weekly by dieticians and research staff who will monitor on-line and by telephone with participants. Reports are to be sent to the DSMB with study progress and adverse events and deviations. We will submit reports to the DSMB as follows: The first non-administrative meeting will occur after the 10th subject (in aggregate from any of the study sites) has been enrolled and reaches the midpoint of the intervention (Diet Week 6, Study Week 10). At this and all subsequent meetings the DSMB will review all available data, aggregate and differential, for safety issues between and within groups. Severity and frequency of the documented AE/UPs will be reviewed at these times. Subsequently, reports will be submitted to the DSMB every 6 months to review safety and efficacy data and any other issues raised by the research team.
23. It was decided that biochemical assays on participants will be conducted at the end of the study in batch assays for economy of finances and effort. We will run batched lipid analyses of all samples when the study is completed, using LC-MS/MS because it is best to run LC-MS/MS assays in one batched analysis, since results can be affected by season, humidity, etc.
24. Prepare first manuscript for publication on the association of baseline PTH characteristics with plasma levels of bioactive lipids in year 5.
25. Continue patient recruitment and enrollment

What opportunities for training and professional development has the project provided?

The research dietician at UNC-Chapel Hill, the head dietician for the study, will train the dieticians at each of the other sites. There is a site visit scheduled for early November at UNC for the dieticians and study RAs to see a similar study in process. Additionally, training videos and reviews of dietary sessions are scheduled between the head study dietician and the dietician at each site.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

Recruit and enroll study participants and execute the protocol.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

As noted earlier in this annual report and prior quarterly reports, there has been a significant delay in IRB approvals for this study through the multi-site study IRB process since the termination of IRBNet. This has significantly delayed launching of this study. We do not anticipate further study Regulatory delays now that we have full regulatory approvals in place.
There has also been a delay in rapid recruiting at WRNMMC after the retirement of the active duty dietician in JUN 2017. A NICoE dietician has just been identified and the security clearance and hiring process at WRNMMC has been initiated with expectation that the dietician will be on board in JAN 2018 and available to perform as the WRNMMC study dietician shortly thereafter.

Changes that had a significant impact on expenditures

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals.

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications.

Nothing to Report.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers, and presentations.

Nothing to Report.

- **Website(s) or other Internet site(s)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Kimbra Kenney MD
Project Role:	Grant PI
Nearest person month worked:	1.2
Contribution to Project:	Dr. Kenney assumed role of PI and directed development and submission of protocol through the WRNMMC multi-site eIRB, IRIS
Funding Support:	HJF through 31 May 2016 and DoD civilian employee from 1 June 2016
Name:	Keturah Faurot PA, PhD
Project Role:	UNC AI
Nearest person month worked:	2
Contribution to Project:	Dr. Faurot developed and submitted UNC protocol, established study DSMB and developed CRFs for the study
Funding Support:	HJF

Name:	Chris Ramsden MD
Project Role:	NIH PI
Nearest person month worked:	1.2
Contribution to Project:	Dr. Rasmden developed submission of exempt protocol through the NIH IRB
Funding Support:	Federal employee
Name:	Wesley Cole, PhD
Project Role:	WAMC PI
Nearest person month worked:	1
Contribution to Project:	Dr. Cole developed and submitted WAMC protocol,
Funding Support:	HJF
Name:	Melissa Guerra, MD
Project Role:	FBCH PI
Nearest person month worked:	0.5
Contribution to Project:	Dr. Guerra will lead the study at FBCH.
Funding Support:	Federal employee
Name:	Beth MacIntosh
Project Role:	UNC AI and study dietician
Nearest person month worked:	1
Contribution to Project:	Ms. MacIntosh assisted with dietician portions of study protocols, participated in monthly conference Calls, and is training study dieticians
Funding Support:	HJF
Name:	Carol Moore MA, CCRC
Project Role:	USUHS AI and Senior Study Manager
Nearest person month worked:	2
Contribution to Project:	Ms. Moore assumed primary role of protocol submission and WRNMMC IRB navigation
Funding Support:	HJF
Name:	Cora Davis, BA
Project Role:	USUHS AI and Research Assistant
Nearest person month worked:	1
Contribution to Project:	Assisted Ms. Moore in protocol submission and navigation
Funding Support:	HJF

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel

The PI has changed twice at FBCH in the past year.

since the last reporting period?

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: NA

QUAD CHARTS: NA

9. APPENDICES: NA